Combat Wound Initiative Program

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ABSTRACT The Combat Wound Initiative (CWI) program is a collaborative, multidisciplinary, and interservice public–private partnership that provides personalized, state-of-the-art, and complex wound care via targeted clinical and translational research. The CWI uses a bench-to-bedside approach to translational research, including the rapid development of a human extracorporeal shock wave therapy (ESWT) study in complex wounds after establishing the potential efficacy, biologic mechanisms, and safety of this treatment modality in a murine model. Additional clinical trials include the prospective use of clinical data, serum and wound biomarkers, and wound gene expression profiles to predict wound healing/failure and additional clinical patient outcomes following combat-related trauma. These clinical research data are analyzed using machine-based learning algorithms to develop predictive treatment models to guide clinical decision-making. Future CWI directions include additional clinical trials and study centers and the refinement and deployment of our genetically driven, personalized medicine initiative to provide patient-specific care across multiple medical disciplines, with an emphasis on combat casualty care.

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14. ABSTRACT

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INTRODUCTION

The combined effects of blasts, high-energy penetrating fragments, and burns from explosive devices contribute to a high incidence of multiple, penetrating, and complex wounds to the extremities and cause extensive soft tissue damage and bone destruction. In the cohort of patients with such injuries, the principal aim of wound care is to reduce the amount of time necessary for wound closure, decrease the rate of infection, and reduce scarring that may be functionally limiting. Innovative approaches to wound healing and tissue regeneration are needed for combat wounds that are typically extensive and difficult to treat with conventional surgical and therapeutic techniques. As such, the primary aim of combat casualty care is to facilitate a patient's safe and rapid return to functional existence and military duty through the preservation of life, limb, and function. Toward that end we established the interservice Combat Wound Initiative (CWI) program. In this review we outline the program, highlight results obtained from this effort, and discuss our vision of the future of personalized care within the Department of Defense (DoD).

METHODS

Program-Specific Aims

The CWI is a collaborative, multidisciplinary, interservice program that has partnered with leaders in wound care and research to provide state-of-the-art, complex wound care through targeted clinical and translational research, incorporating advanced technology and treatment, tissue banking, and bioinformatics. This private/public partnership addresses unmet needs in combat casualty care by providing an integrated approach to wound healing. Specifically, the partnership was established to:

(1) Deliver the highest quality advanced wound care to our healthcare beneficiaries.
(2) Conduct first-rate integrated basic, clinical, and translational research, which seeks to define the most efficacious and cost-effective wound treatment strategies.
(3) Advance personalized medicine within the context of complex wound care.
(4) Integrate data from all research efforts from which to develop and validate clinically useful decision support tools (predictive models of wound healing).
(5) Promote the image of military medicine.
(6) Enhance communication and collaboration and foster lasting strategic partnerships across military service and civilian institutional lines.

To accomplish these goals the CWI seeks to achieve five specific objectives:

(1) Critically evaluate new technologies for the treatment of acute and chronic wounds in the context of institutional review board-approved clinical trials at affiliated centers of excellence including the interservice military Complex Wound and Limb Salvage Center.
(2) Identify mechanisms and predictors of wound healing on the basis of studies of biomarker expression in blood, local wound effluent, and multigene expression profiles of wound tissue.
(3) Develop and maintain a combat wound biorepository of human serum, wound effluent, and tissue as well as debrided bone and resected heterotopic ossification for translational research.
(4) Maintain a comprehensive database to integrate all CWI data elements.
(5) Apply a new analytical platform, Bayesian belief networks, to model complex data sets with the goal of being able to predict wound outcomes on the basis of clinical and molecular data and to develop and validate prospectively these decision support tools or predictive models.

These elements will facilitate the development of individualized care of casualties in an era of personalized or information-based medicine.

This bench-to-bedside strategy is the hallmark of the program and is aimed at providing the best possible care of wounded patients. Clinical centers playing a significant role in this unrivaled collaborative research effort are:

— Walter Reed Army Medical Center, Washington, DC
— National Naval Medical Center, Bethesda, Maryland
— Naval Medical Research Center, Silver Spring, Maryland
— Armed Forces Institute of Pathology, Washington, DC
— Brooke Army Medical Center, Fort Sam Houston, Texas
— Uniformed Services University of the Health Sciences, Bethesda, Maryland
— Johns Hopkins University, Baltimore, Maryland
— Georgetown University Medical Center, Washington, DC
— University of Florida College of Medicine, Gainesville, Florida
— North Florida/South Florida Georgia Veterans Health System
— Memorial Medical Center–Conemaugh Health Systems, Johnstown, Pennsylvania
— University of Alabama at Birmingham, Alabama
— Hadassah Hebrew University Medical Center, Mount Scopus, Jerusalem, Israel
— University of Missouri, Columbia, Missouri
— University of Mississippi, University, Mississippi

The current mechanisms of wounding in Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) demand innovative approaches to wound care and the development of advanced treatment methods that promote healing of combat wounds, which are typically extensive due to considerable soft tissue disruption and contamination and are unsuitable for conventional dressings.

A crucial part of the CWI is the development and testing of new and innovative technologies for treating combat wounds and tissue regeneration. Current research focuses on adjunctive wound healing modalities such as extracorporeal shock wave therapy (ESWT) in animal models and clinical trials, as well as the validation of biomarkers to define timing of wound closure or coverage and predict overall wound healing and casualty outcome.

Informatics and Machine-Learning Support

We turned to machine learning algorithms using Bayesian classification systems for a number of important reasons in an effort to develop a predictive model, which could serve as a clinical decision support tool in the management of complex war wounds. Bayesian belief networks (BBN) provide multivariate mapping of complex data, can model any scenario within the data space, provide posterior probability estimates given a priori data, are transparent (providing a graphical explanation to the answers provided within model structure), and permit cross-validation.

Machine learning is a field of computer science that uses intelligent algorithms to allow a computer to mimic the process of human learning. These algorithms allow the computer to learn dynamically from the data that resides in a "data warehouse." The machine learning algorithms automatically detect and identify significant relationships between variables without the need for human interaction. This allows for the processing of vast amounts of complex data quickly and easily. The two most common goals of machine-learned BBNs are: gaining insights about the domain or "data warehouse," and making predictions on the basis of the given data.

Predictions are made about unobserved data via probabilistic inference. That is, given a set of observations and data, Bayesian networks find the conditional probability distributions of one or more of the remaining attributes or conditions, even if the user only possesses partial information. Hence, a BBN allows one to predict the likelihood of the various states in nonobserved variables on the basis of the states of observed variables. One of the additional benefits of full Bayesian networks is that the completed networks include conditional dependence assumptions between otherwise independent variables. This allows the network to control for the confounding variables and biofeedback mechanisms that are inherent in biologic systems.

RESULTS

Translational Research—Bench

Shock Wave Therapy in Burns

Severe cutaneous burns are associated with unresolved inflammatory response maintained by burn surface eschar, bacterial burden in the burn wound, and white blood cell proteolytic activity. These factors collectively perpetuate the inflammatory state and retard normal healing responses and can lead to further soft tissue damage. Extracorporeal shock wave therapy (ESWT) is a well-established medical therapy that has been shown to improve healing in human burns and difficult-to-heal soft tissue wounds.[1] The mechanism of action of shock waves in soft tissue remains poorly understood. As part of our bench-to-bedside approach we investigated the role of ESWT on the early proinflammatory response using a severe, full-thickness 15% total body surface area skin burn wound in a mouse model (Institutional Animal Care and Use Committee approved NMRC protocol no. K01-08).

Various quantitative outcome assessments were made to include wound inflammatory cell infiltrate and expression of genes known to be involved in acute inflammation and wound healing.[2] The findings of this study demonstrated that a single shock wave treatment following burn injury has no adverse effect on the rate of severe burn wound closure, significantly reduces inflammatory cell infiltrate, and is associated with global suppression of biomarkers including chemokines, proinflammatory cytokines, and matrix metalloproteinases.

This rapid and widespread suppression of key local regulators of phase-specific wound healing, particularly proinflammatory mediators and inflammatory response in a severe burn after a single treatment with shock waves, has important clinical implications and supports early clinical studies suggesting favorable healing responses to shock wave therapy. Clinical success to date of shock waves in treating severe burns and complex wounds coupled with the mechanistic data demonstrated here supports a biological basis for a positive treatment effect of shock waves.

Angiogenic Response to Shock Wave Therapy in Skin Grafts

From our research, two interesting findings have clearly demonstrated that ESWT produces significant anti-inflammatory properties in acute burn wounds. These findings include: a significant decrease in proinflammatory chemokine and cytokine synthesis at the wound site and a marked reduction in inflammatory leukocyte recruitment to the treated burn. Additionally, previous research suggests that therapeutic shock waves stimulate early expression of angiogenesis-related growth factors associated with proangiogenic responses and improved local blood flow and tissue repair. On the basis of these molecular and cellular findings, we decided to examine the effect of ESWT on angiogenesis in a small animal model.[3,4,5,6]

Using a small animal skin graft model we demonstrated that a single shock wave administered at the time of skin grafting promoted angiogenesis at the macroscopic, microscopic, and cellular levels. In addition to the significant enhancement of recipient skin graft revascularization, a profound early increase in proangiogenic response and significant reduction in delayed proinflammatory response was observed after a single shock wave treatment postgrafting at the gene transcript level. Skin grafts are used frequently in surgical practice to provide definitive wound coverage. Revascularization of a skin graft occurs through a process known as neoangiogenesis, which is essential for graft integration, viability,

and durability. Improved treatment modalities are needed to address the problem of threatened soft tissue viability, particularly in chronic wounds and remote aspects of skin flaps compromised by ischemic necrosis. The mechanisms of therapeutic shock waves is not completely understood, but mechanistic and clinical data suggest that ESWT is a safe, feasible, and clinically useful wound therapy adjunct for various acute and chronic nonhealing or ischemic wounds. We have capitalized on these preclinical findings with the initiation of a clinical trial to assess the effects of ESWT in combat wounds and burns as described below.

Translational Research—Bedside

Clinical Applications of Therapeutic Shock Wave Therapy for Wounds

CWI clinical trials are designed to evaluate the efficacy of advanced therapies in human soft tissue wound and fracture healing. Shock wave therapy devices deliver energy to the wound with favorable, though complex, interrelated and incompletely understood cellular biochemical pathways. Therapeutic shock waves are currently undergoing clinical evaluation as a means to facilitate tissue repair in acute, and nonhealing or chronic wounds, regeneration in burns and autologous split thickness skin graft donor sites. Recognizing that therapeutic shock waves have characteristics that make them clinically useful—noninvasiveness/minimal patient risk, ease of tissue application, absence of drug interactions, cost effectiveness, and seemingly comparable efficacy to existing therapies for soft tissue indications—we undertook a phase II prospective clinical trial to determine the feasibility and safety of unfocused shock wave wound therapy.[1] Patients with acute and chronic nonhealing wounds of various causes were enrolled including: failed primary surgical closure, traumatic wounds, arterial and venous insufficiency ulcers, pressure sores, and partial thickness burns. Patients underwent standard wound bed preparation and moist dressings, in addition to ESWT (0.1 mJ/mm^2; 5 pulses/second; 100 pulses/cm^2; weekly and then every 2 weeks). Of the 208 study subjects enrolled, 32 (15%) dropped out of the study following first ESWT and were analyzed on an intent-to-treat basis as failures. Three-fourths of the patients enrolled had complete wound healing (100% wound epithelialization). Over a 6-week follow-up period, no patient suffered treatment-related toxicity, infection, or deterioration of any shock-wave-treated wound.

Wound size (surface area) and duration were found to be independent predictors of complete wound healing on multivariate analysis. Wound healing response was stratified according to these variables (as shown in Table I).

Although there was no statistically significant difference in complete wound healing time among the following three groups: ≤10 cm^2 and ≤1 month versus ≤10 cm^2 and >1 month versus >10 cm^2 and ≤1 month ($p = 0.49$), complete healing was significantly less likely and healing time prolonged in patients with large (>10 cm^2) chronic (>1 month) wounds ($p < 0.01$).

In summary, this prospective feasibility trial conducted in patients with acute and chronic soft tissue wounds treated with surgical debridement, outpatient unfocused ESWT, and standard moist wound dressings demonstrated complete healing in 156 of 208 (75%) cases. Predictors of positive healing response were wound size (≤10 cm^2) and duration (≤1 month). No shock-wave treatment-related toxicity, infection, or wound deterioration was identified in this study.

Clinical experience to date with shock wave therapy for soft tissue wounds finds the device to be a safe, noninvasive, painless treatment method to reduce bacterial load in wounds and facilitate blood vessel in-growth and soft tissue healing. Our phase II clinical trial served as the basis of an ongoing randomized controlled trial evaluating shock wave therapy in patients with acute traumatic wounds and burns of the extremity

TABLE I. Comparisons of Wound Type, Number of Shock Wave Treatments, and Wound Healing Response According to Wound Size (≤10 and >10 cm^2) and Wound Duration (≤1 and >1 Month)

	≤ 10 cm^2 ≤ 1 Month $n = 116$		≤ 10 cm^2 > 1 Month $n = 35$		> 10 cm^2 ≤ 1 Month $n = 41$		> 10 cm^2 > 1 Month $n = 7$		
Characteristic	No.	%	No.	%	No.	%	No.	%	p value
Etiology of Wound									0.001
Disturbed Healing	49	62.0	12	15.2	17	21.5	1	1.3	
Post-traumatic	41	64.0	3	4.7	20	31.3	0	0.0	
Venous Stasis Ulcer	4	16.0	15	60.0	1	4.0	5	20.0	
Decubitus Ulcer	8	66.7	2	16.7	1	8.3	1	8.3	
Plaster Cast Pressure Sore	6	85.7	0	0	1	14.3	0	0	
Arterial Insufficiency Ulcer	2	40.0	3	60.0	0	0	0	0	
Burn	6	85.7	0	0	1	14.3	0	0	
ESWT Treatments									0.001
Mean	2.3 ± 0.2		3.6 ± 0.3		3.4 ± 0.3		5.6 ± 0.7		
Healing									0.001
Incomplete Epithelialization	14	12.1	13	37.1	12	29.3	5	71.4	
Complete Epithelialization	102	87.9	22	62.9	29	70.7	2	28.6	
Time to Healing, Days	39.4 ± 4.7		42.5 ± 10.1		51.4 ± 8.8		164.5 ± 33.4		0.009

to determine whether this therapeutic modality meets combat casualty care requirements for complex wound treatment.[1] The multiwave device being tested contains a parabolic reflector in the shock wave therapy head, which allows delivery of unfocused waves of acoustic energy over a broad target wound surface area with reduced depth of penetration allowing treatment without the need for anesthesia. The primary aim of this phase III trial is to conduct definitive field testing to determine whether shock wave therapy significantly improves wound healing over current standards of care. Patients with acute traumatic extremity wounds are stratified according to wound severity and randomized into one of two study groups: standard of wound care versus standard of care + ESWT every 2 weeks up to four treatments. The primary outcome variable is time to complete wound healing or closure. Secondary outcome variables include quality of life, length of hospital stay and procedure avoidance, and the appraisal of the effect of ESWT on local wound bacteria, serum, wound fluid, and wound tissue biomarkers.

Biomarkers in Combat Casualty Care

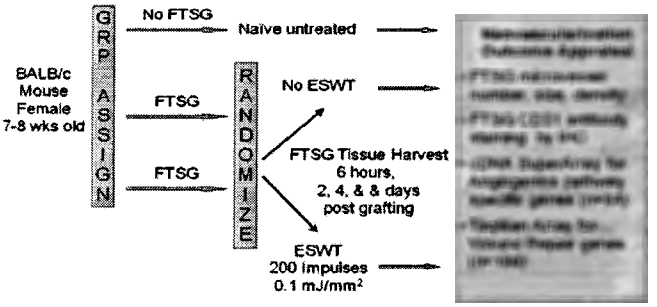
A biomarker is an anatomic, physiologic, biochemical, or molecular parameter that indicates, or is associated with, an alteration in physiology and is of clinical significance. Given the advances in combat casualty care, we have witnessed the emergence of a large military healthcare population composed of surviving casualties with devastating war wounds, traumatic amputations, and penetrating and closed traumatic brain injuries. Given the complexities of local and systemic responses to wounding, predictive treatment-directing models represent an unmet need in combat casualty care. Such models could guide individualized treatment decisions regarding the surgical management of wounds and estimate overall outcome of patients on the basis of casualty-specific factors in wounded service members with complex traumatic wounds. Typically, the decision to proceed with definitive delayed primary closure of war wounds or coverage with skin grafts or flaps is largely based on gross physical findings; a clean and viable wound bed in a stable patient without obvious signs of active infection or sepsis suggests that the time is "right" for closure or coverage.

Admittedly there is considerable intraobserver variability in terms of complex wound and patient assessment. Despite assiduous and repeated operative wound debridement, pulse lavage, antibiotic and mechanical therapy, up to 25% of war wounds in our experience dehisce partially or fully after closure or coverage. The variability in time to closure on the basis of these largely subjective criteria leaves some clean wounds open to undergo perhaps unwarranted surgical and anesthetic interventions, exposing patients to additional potential surgical morbidity and anesthesia risk, and leaves medical centers open to unnecessary healthcare resource utilization. Gross morphology of the wound is a nonspecific predictor of wound outcome.

A number of factors are considered in the decision to definitively close a wound in addition to patient general condition and gross wound appearance: location of the wound, adequacy of wound bed perfusion, presence of local or systemic infection, nutritional status, and nonspecific serum markers of inflammation such as white blood cell count (WBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). However, clinical decision algorithms for wound closure on the basis of these measures are ill-defined.[7]

Although a number of clinical factors are considered in the decision to definitively close or cover a wound, no one existing criterion is sufficiently predictive of ultimate wound healing to permit the utilization of an objective, evidence-based decision algorithm. In fact, the frequently studied, nonspecific serum factors or parameters such as WBC, ESR, and CRP, are generally not useful for surgical decision making. These conventional circulating acute phase reactants fail to provide data in the perioperative period useful to surgical decision making. In fact, the complexity of wound healing, which involves the intricate interplay and dynamic coordination between cytokines and chemokines in the wound and those in the systemic circulation makes isolation of a single surrogate biomarker predictive of wound healing unlikely. The molecular landscape of the complex wound is the principal determinant of the likelihood of durable, event-free wound healing. When the complex coordinated biology of wound healing is disrupted by coexisting disease, pharmaceuticals, or by the complexity of wounds exceeding the ability of these repair mechanisms, the normal pattern of wound repair fails and a chronic inflammatory state is created that further impairs healing. Objective criteria and clinical decision support algorithms to define the appropriate timing of wound closure and reliable predictors of wound outcome represent an unmet need in combat casualty and complex civilian trauma care.

Recognizing that cytokines and chemokines orchestrate the progression of wound healing and that they are fundamental components to the cellular and biochemical events that occur during acute wound healing, we sought to determine whether these effectors could be measured in serum and wound effluent using modern molecular techniques. We have completed a pilot study (NNMC.2005.069) with the intent to develop an objective means of determining the likelihood of complex wound healing, hence the timing of traumatic war wound closure. That study demonstrated the feasibility of multiplex



FTSG: Full thickness dorsal skin isograft, 3 x 3 cm

FIGURE 1.

(human multiplex cytokine detection systems) quantification of wound effluent cytokine and chemokine expression in acute war wounds at time of wound closure.[8] Among the 23 wound effluent chemokines and cytokines analyzed, three emerged as potential biomarkers. War wounds that dehisced were associated with elevated procalcitonin (ProCT), decreased regulated on activation, normal T expressed and secreted (RANTES) protein, and decreased interleukin-13 (IL-13) concentrations. These preliminary results suggest that serum effluent biomarker analysis may provide the much needed objective predictors of acute wound healing.

Advances in the field of combat-related wound healing remain limited in part by an incomplete understanding of the fundamental cellular and molecular mechanisms driving the normal healing process versus those that contribute to dysregulated wound healing responses, often resulting in difficult to heal, chronic wound states. Cytokine and chemokine expression may provide these much needed insights into the molecular pathogenesis of acute wound failures. The balance between pro- and anti-inflammatory mediators during wound repair is crucial to achieving tissue homeostasis following injury.[9,10] In fact, chronic wounds remain locked in a state of intractable inflammation. Acute wound failures are likely related to similar detrimental inflammatory responses to injury. What is more, a systemic inflammatory state appears to contribute to dysregulated local wound inflammatory responses, a link that our group has shown for the first time at the molecular level.[11] We have recently demonstrated the feasibility and utility of a decision support algorithm for objective wound closure based on serum and wound effluent cytokine and chemokine biomarker expression using probabilistic (Bayesian belief network) modeling (Fig. 2).

DISCUSSION

Personalized Medicine: Integration Into Combat Wound Care

Personalized medicine[12] is a genotype-centered, or information-based approach to medicine that emphasizes a proactive treatment process regardless of whether the disease is behavioral or genetic in origin. Today, medicine is product-based: a cardiologist prescribes a drug for perioperative cardiopulmonary risk reduction; a surgeon conducts an operation and implants a prosthetic. What is needed, and what the future holds, is a process-oriented medical system.

Personalized medicine is a process, not a product by which variations—both in the patient and in the molecular underpinnings of the disease itself—can be used to develop new treatments and identify subgroups of patients for whom the new treatments will work best and avoid the risk of treatment for patients that will not respond to it. Genetic information can be used to determine which groups of patients are more prone to the development of certain diseases and, ideally, will aid in the selection of lifestyle changes or treatments that can delay onset of a disease or reduce its impact. The major impact of personalized medicine is that physicians can design treatment strategies

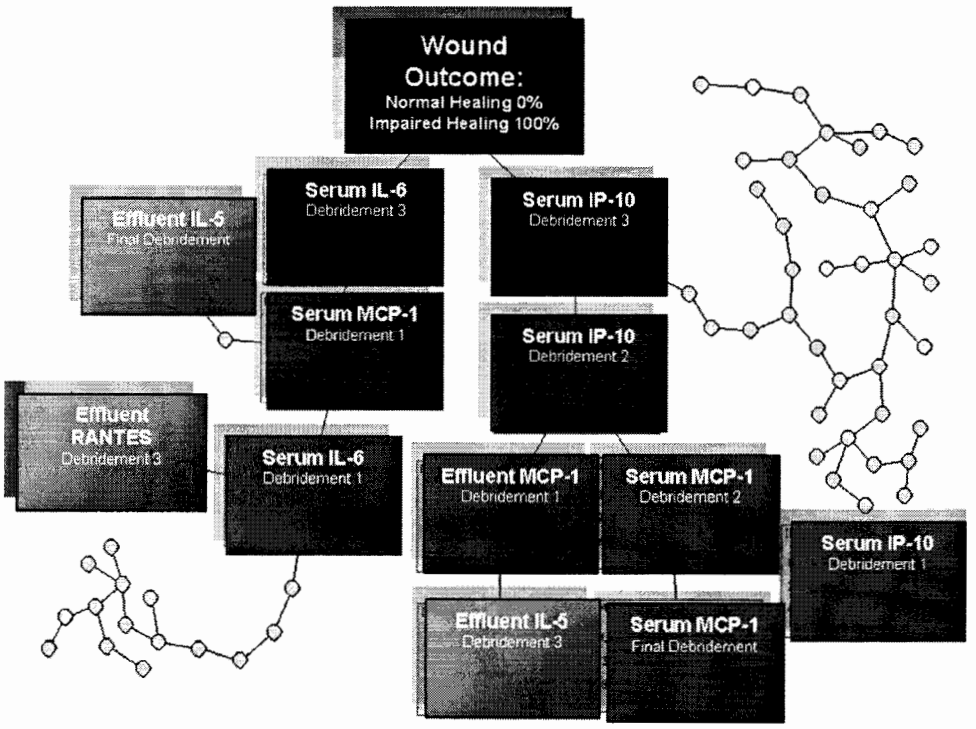


FIGURE 2.

on the basis of their patient's genetic make-up. Instead of prescribing medication developed in the traditional method of empiric observation and disease mechanism, physicians can optimally manage their patient's diseases by precise dosing that is based on complex software-aided algorithms that take into account the patient's age, gender, weight, and genotype.

Personalized medicine is poised to transform healthcare over the next several decades. New diagnostic and prognostic tools will increase our ability to predict the likely outcomes of drug therapy, while the expanded use of biomarkers may result in more focused and targeted drug development. Personalized medicine also offers the possibility of improved health outcomes and has the potential to make healthcare more cost effective.

Computers and computer software have the ability to support clinical decision making through indexing and cross-referencing data in a way most human minds cannot. Analytical software engines provide a mechanism to codify information, validate models of relationships between important variables, and permit access to vast amounts of information via an easy-to-use interface that characterizes critical relationships between clinical variables, thus ultimately supporting complex decision making.

Although personalized medicine has been implemented in fields such as oncology and infectious disease, the treatment of trauma and wounds has yet to benefit from this approach. Using advanced data mining and modeling algorithms, we have attempted to address this shortfall by developing an integrated predictive modeling application that allows the clinician to interpret clinical data in the context of large population evidence quickly and automatically with detailed risk stratification and quality estimates. The lack of stratification in care results in the overtreatment of many service men and women, delaying rehabilitation and return to service as well as exposing some patients to the morbidities of a significant hospital stay. We estimate an annual cost savings to a single military treatment facility of $2.2 million, on the basis of reduction of one surgical wound debridement (reduction from 3.5 to 2.5 mean operations per patient), which can be achieved by instituting a personalized medicine approach. Conversely, by directing targeted treatment to casualties with a high risk of impaired healing, outcomes for our most severely wounded can be improved.

As the amount of clinical and diagnostic data continues to grow amid mounting pressures to improve outcomes while controlling cost, evidence-based personalized medicine becomes essential. We are in the process of bringing real-time and information-based medicine to the DoD healthcare system, particularly regarding combat casualty care.

The Combat Wound Initiative program is an active, highly productive translational medicine program. This interservice, collaborative, multidisciplinary program is a private/public partnership of military and civilian leaders who are dedicated to the translation of fundamental research into individualized patient care through the application of advanced therapies and technologies, bioinformatics, biobanking, and personalized medicine. Each of the program's components described in this article have unique capabilities and the very highest military relevance—especially in a time of war. As advances based on these promising findings are implemented in the numerous hospitals and mobile surgical units, the ability to save the lives of service members will be enhanced.

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